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Lung Cancer Case–Control Study of Beryllium Workers

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Background *Cohort mortality studies have found elevated lung cancer mortality among beryllium-exposed workers, but none evaluated the association between beryllium exposure level and lung cancer risk. A nested case–control study of lung cancer within a beryllium processing plant was conducted to investigate the relationship between level of beryllium exposure and lung cancer.*

Methods *Lung cancer cases were identified by mortality follow-up through 1992 of a cohort of male workers at a beryllium alloy production plant. Each of 142 lung cancer cases was age–race-matched to five controls. Calendar-time-specific beryllium exposure estimates were made for every job in the plant and were used to estimate workers' cumulative, average, and maximum exposures. The potential confounding effects of smoking were also evaluated.*

Results *Lung cancer cases had shorter tenures and lower lifetime cumulative beryllium exposures than controls, but higher average and maximum exposures. However, after applying a 10- and 20-year lag, exposure metrics were higher for cases. Odds ratios in analyses lagged 20 years were significantly elevated for those with higher exposure compared to the lowest exposure category. Significant positive trends were seen with the log of the exposure metrics. Smoking did not appear to confound exposure–response analyses.*

Conclusion *Increased lung cancer among workers with higher lagged beryllium exposures and lack of evidence for confounding by cigarette smoking, provide further evidence that beryllium is a human lung carcinogen.* Am. J. Ind. Med. 39:133–144, 2001. *Published 2001 Wiley-Liss, Inc.*†

KEY WORDS: beryllium; lung cancer; case–control study; lagged exposure; smoking confounding

INTRODUCTION

Toxic effects from inhaling beryllium compounds have been known for several decades [Gelman, 1936]. In the United States, dermatitis and acute pneumonitis were first associated with beryllium exposure at refineries during World War II [Van Ordstrand et al., 1945]. Shortly thereafter, cases of chronic beryllium disease (CBD) were found in the fluorescent lamp industry [Hardy and Tabershaw, 1946]. Also, beryllium-containing compounds have been studied extensively and shown to be carcinogenic in animals [Gardner and Heslington, 1946; IARC, 1980]. Lung cancer has been induced in two animal species, rats and monkeys, either by the inhalation or tracheal instillation of beryllium sulfate, phosphate, oxide, and beryl ore particles [Groth, 1980].

As of 1992 when the current study was initiated, a number of mortality studies had been conducted of indi-

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viduals in a registry of beryllium disease cases and beryllium production cohorts [Mancuso and El-Attar, 1969; Mancuso, 1970, 1979, 1980; Infante et al., 1980; Wagoner et al., 1980]; but the epidemiologic evidence for carcinogenicity was considered to be limited [IARC, 1987]. In 1993, the International Agency for Research on Cancer (IARC) re-evaluated beryllium and found the human evidence for carcinogenicity to be sufficient [IARC, 1993]. This finding was based largely on the results of two epidemiologic studies [Steenland and Ward, 1991; Ward et al., 1992].

In a mortality study of individuals in the U.S. beryllium case registry, Steenland and Ward found excess mortality for lung cancer (SMR = 2.00; 95% CI = 1.33–2.89), which was greater for registry members who had acute pneumonitis (SMR = 2.32; 95% CI = 1.35–3.72) than for those with chronic beryllium disease (SMR = 1.57; 95% CI = 0.75–2.89) [Steenland and Ward, 1991]. In a study of seven U.S. beryllium processing facilities, Ward reported a statistically significant excess risk for lung cancer (SMR = 1.26; 95% CI = 1.12–1.42) in the total cohort, with higher lung cancer SMRs at the two oldest plants studied [Ward et al., 1992]. Neither of these studies was able to assess quantitatively the relationship between intensity of beryllium exposure and mortality from lung cancer. An Advisory Committee to the Beryllium Industry questioned the IARC determination of sufficient evidence for the carcinogenicity of beryllium in humans, suggesting the existing epidemiologic studies did not adequately control for smoking, failed to demonstrate an exposure–response pattern, and did not consider sulfuric acid mist exposure as an explanation for the elevated lung cancer SMR at the Lorain, Ohio plant [BISAC, 1997].

We present the results of a case–control study conducted at one of the beryllium processing facilities in the seven-plant cohort mortality study. This plant was selected because it had both a large number of lung cancer cases, and adequate personnel and beryllium exposure records to construct historical exposure estimates. The objective of this study was to investigate the relationship between beryllium exposure level—and type of beryllium exposure—and lung cancer. The study also addressed the potential confounding effect of cigarette smoking and other chemical exposures at the study plant.

METHODS

Lung cancer cases and controls were identified within a cohort of 3,569 male workers employed at a beryllium processing facility located in Reading, Pennsylvania between January 1, 1940 and December 31, 1969. Details of cohort ascertainment and follow-up through 1988 have been published previously [Ward et al., 1992]. For the purposes of the case–control study, vital status follow-up was extended through December 31, 1992. For each case who died with lung cancer listed as the underlying cause of death on the death certificate, five controls were selected by incidence density sampling and were required to have survived to at least the age at which the index case died and to be of the same race. Cases were excluded from being their own control and selection was done with replacement [Beaumont et al., 1989]. Work histories were updated through 1992 and coded using a list of jobs and departments developed by review of company and union records, information in NIOSH and Department of Energy archives, and the published literature. All work history data were entered blindly, without knowledge of case or control status.

Work history records were linked to a file of quantitative, time-specific exposure estimates for each job and department to generate cumulative, average, and maximum beryllium exposure metrics for each worker, as well as to determine each worker's exposure status with respect to beryllium fume or dust, exposure to various chemical forms of beryllium, and exposure to other chemical agents. Exposures for controls were truncated at the age of death of the matched case. Details of constructing the job-exposure matrix are provided in another paper [Sanderson et al., 2001].

In addition to duration of employment, three quantitative exposure metrics were calculated for the cases and controls. Cumulative beryllium exposure was calculated by summing the products of the number of days of employment in each job the workers held times the estimated annual average beryllium exposure for the job on those specific days. Cumulative beryllium exposure is expressed in units of micrograms of beryllium per cubic meter days ($\mu g/m^3$ days). Average exposure was calculated by dividing the cumulative exposure by the total number of days employed, and is expressed in units of $\mu g/m^3$. Maximum exposure was estimated to be the highest time-weighted average (TWA) exposure of any job the worker held, regardless of duration [Checkoway and Rice, 1992]. The effects of duration and age at which the worker experienced the maximum exposure were also evaluated in data analysis. To discount exposures which may not have contributed to causing lung cancer because they occurred after cancer was already induced, tenure and the three quantitative exposure metrics of the cases and controls were lagged 10 and 20 years [Checkoway et al., 1989].

Based on their job-department assignments, cases and controls were assigned to dichotomous categories of ''ever'' and ''never'' exposed to each of the types of beryllium encountered in the plant—beryl ore, beryllium fluoride, beryllium hydroxide, beryllium oxide, beryllium–copper alloy, and beryllium–aluminum alloy. In addition to the ever/never categories of exposure, the number of days of exposure, cumulative exposure, average exposure, and maximum exposure metrics for the types of beryllium were

also calculated for each case and control. These exposure metrics were also lagged 10 and 20 years.

Besides the chemical types of beryllium compounds, the association of other chemical agents which may be toxic to the lung were determined for each job at the Reading plant. In particular, each department and job combination was evaluated to determine whether it involved potential exposure to fluorides, copper, aluminum, cadmium, chromium, nickel, nitric acid aerosol, oxides of nitrogen, or welding fume and gases. There was no potential exposure to sulfuric acid at the study plant because it used a fluoride rather than a sulfate extraction process. The cases and controls were assigned to dichotomous categories of ''ever'' and ''never'' exposed to these chemical agents and their number of days of exposure to these potential confounders were calculated (lagged and unlagged).

SAS [SAS Institute Inc., 1988] was used for all statistical analyses. The frequency distributions of the cases and controls by employment within particular departments or work areas were compared using the Cochran–Mantel–Haenszel χ^2-test for matched data [Mantel, 1963; Landis et al., 1978]. Since the exposure metrics of the cases and controls were skewed and not normally distributed, the metrics were transformed to their natural logarithms. The geometric means of the beryllium exposure metrics—lagged and unlagged—of the cases and controls were compared using general linear models (GLM) analysis for matched data.

Conditional logistic regression was used to estimate the odds ratio of exposure between the cases and controls by quartiles of beryllium exposure and continuous exposure–response [Kleinbaum et al., 1982]. Continuous exposure–response analysis also included quadratic and logged exposure variables. Conditional logistic regression was used to estimate the lung cancer odds ratio for ever having been exposed to the various chemical forms of beryllium and potential confounders. Smoking is an important risk factor for lung cancer. But to be a confounder for an internal exposure–response analysis, cigarette smoking must be differentially distributed by level of beryllium exposure [Axelson, 1989]. The only data available on the smoking habits of the cohort came from a health survey conducted in 1968 by the U.S. Public Health Service (USPHS). This dataset included information on whether workers were non-smokers, cigarette smokers, ex-smokers, or smokers of pipes or cigars; when they began smoking; and, how much they smoked per day. These data covered only about 10% of the cohort, very few of whom were employed in the 1940s and 1950s when most of the lung cancer cases and controls began employment.

In order to evaluate potential confounding by cigarette smoking, age-adjusted exposure estimates were generated for the workers who participated in the 1968 USPHS study, by smoking status. Confounding by professional status was evaluated by stratifying workers into ''professional'' and ''non-professional'' categories. Professional workers were defined as employees holding sales, engineering, research and design, plant management, and administration jobs for greater than half of their tenure at the Reading plant. Since it appeared that an association between smoking and beryllium exposure was related to professional status, beryllium exposure analyses were repeated after excluding professionals. An alternative analytic approach, which was to include professional status in the logistic models, was considered inappropriate because of the strong association between professional status and beryllium exposure. Stratification on a variable highly associated with exposure could distort any estimate of the exposure–response trend.

RESULTS

The lung cancer mortality rate for the Reading plant cohort, updated through 1992, was 1.22 (95% confidence interval (CI) = 1.03–1.43). This mortality rate remained relatively the same as found in the original cohort study followed through 1988 (SMR = 1.24; 95% CI = 1.03–1.48) and very similar to the lung cancer mortality rate for all plants combined (SMR = 1.26; 95% CI = 1.12–1.42) [Ward, et al., 1992].

A total of 142 lung cancer cases and 710 controls were included in the case–control analysis; 93% of the cases were white and the average age at hire was 33 and 37 years for the cases and controls, respectively. The majority of cases and controls were first hired during the 1940s, with $\approx$60% hired during 1941–1945. The average tenure was 3.7 years (median = 5 months) for the cases and 5.5 years (median = 11 months) for the controls, but almost two-thirds of the cases and over half of the controls were employed at the plant for <1 year.

There were no striking differences between the proportion of cases and controls who had ever worked in selected departments or work areas; although cases had more frequently served as general labor and maintenance workers than the controls (Table I). General labor and maintenance workers often encountered some of the highest beryllium exposures. Comparison of the unlagged exposure metrics for cases and controls revealed that cases had significantly lower tenures and nearly significantly lower cumulative exposures (Table II). However, when the duration of exposure and cumulative exposure metrics were lagged 10 and 20 years, the geometric mean tenures and cumulative exposures of the cases were higher than those of the controls. The geometric mean average and maximum exposures of the cases were greater than for the controls, and the difference was highly significant ($P < 0.01$) when the exposure estimates were lagged 10 and 20 years (Table II).

Table III shows analyses by quartiles of the tenure, cumulative, average, and maximum beryllium exposure

TABLE I. Frequency of Cases and Controls Who Ever Worked in Selected Departments (Beryllium Workers Case–Control Study, USA)

	0 Lag		10-Year lag		20-Year lag	
Department	**Cases (%)**	**OR**	**Cases (%)**	**OR**	**Cases (%)**	**OR**
Ore handling	2.8	1.33	2.8	1.43	2.1	1.50
Hydroxide production	13.4	1.04	12.7	1.07	11.3	1.15
Oxide production	7.0	0.51	7.0	0.59	6.3	0.64
Arc furnace	8.5	0.83	7.8	0.79	6.3	0.76
Melt and cast	15.5	1.20	15.5	1.35	12.0	1.30
Ajax furnace	4.2	1.67	4.2	1.77	2.8	1.43
Foundry	2.1	0.50	2.1	0.58	1.4	0.48
Machine shop	12.7	1.26	12.7	1.45	11.3	1.60
Hot mill	21.8	0.91	21.8	1.10	18.3	1.13
Cold mill	10.6	1.41	9.9	1.48	8.5	1.71
Rod, wire, and extrusion	4.9	0.97	4.9	1.22	3.5	1.32
Annealing and heat treatment	2.8	0.42	2.8	0.57	1.4	0.39
Slitting	6.3	0.94	6.3	1.16	4.2	0.97
Pickling and plating	7.8	0.85	7.8	1.10	4.9	1.07
Inspection	1.4	0.63	1.4	0.67	0.7	0.39
Shipping and receiving	4.2	0.81	4.2	1.03	3.5	1.32
Labs	3.5	0.50	3.5	0.50	3.5	0.50
Maintenance	31.7	1.34	31.7	1.56*	26.8	1.60*
General labor	7.0	1.37	7.0	1.60	6.3	2.32*
Furnaces	23.2	1.10	23.2	1.10	21.8	1.03
Oxide side of plant	25.4	0.82	25.4	0.83	25.4	0.85
Mill side of plant	39.4	1.11	39.4	1.14	38.0	1.10
Sales and administration	12.0	0.95	12.0	1.01	9.9	0.90

*$P < 0.05$.

metrics lagged 0, 10, and 20 years. The odds ratios decreased with increasing unlagged tenures, indicating that the cases tended to have lower unlagged tenures than the controls. However, as tenure was lagged the decreasing trend was not observed; when tenure was lagged 20 years, the odds ratio was significantly elevated in the second and third quartiles, indicating that a greater proportion of cases was in the second and third tenure quartiles, although not the fourth. Similar results were found comparing the cases and controls by cumulative exposure quartiles—the cases had lower unlagged cumulative exposures, but when exposures were lagged 20 years the odds ratios for the second, third, and fourth quartiles were significantly elevated.

No decreasing trend in odds ratios appears with the unlagged intensity of exposure metrics—average and maximum exposure (Table III). When the intensity exposure estimates were lagged 10 years, significantly elevated risk was seen for all quartiles compared to the first. When intensity of exposure estimates were lagged 20 years, the odds ratios were elevated for all quartiles compared to the lowest one, but only the second and third quartiles were significantly higher.

A monotonic increase in the ORs with increasing exposure was not observed across the quartiles; the odds ratios of the lagged second, third, and fourth beryllium exposure quartiles were usually above 1.0, but did not exhibit a linear exposure–response pattern. Continuous exposure–response analysis of the logged exposure variables showed a significant negatively sloping relationship with the log of unlagged tenure and a significant positive association with the log of tenure lagged 20 years (Table IV). A significant positive association was also shown with the log of cumulative exposure lagged 10 years and the log of cumulative exposure lagged 20 years. A strong positive association was found with the log of the average and maximum exposure estimates lagged 10 and 20 years. No association was found with the unlagged cumulative, average, or maximum exposures estimates. When logs were not taken, very few associations were found whether using linear or quadratic analysis.

The average and maximum exposures of the cases and controls were also compared by the following categories: <2 $\mu g/m^3$ (which is the Occupational Safety and Health Administration's permissible exposure limit for beryllium);

TABLE II. Comparison of Geometric Mean Exposure Metrics of Cases and Controls by Various Beryllium Exposure Estimates (Beryllium Workers Case–Control Study, USA)

	Cases n = 142	Controls n = 710	
Exposure parameter	**GM[a] (GSD)[b]**	**GM (GSD)**	***P*-value**
Tenure (days)	202.1 (9.4)	328.0 (9.4)	0.019
Tenure lagged 10 years (days)	178.4 (19.7)	133.0 (19.7)	0.284
Tenure lagged 20 years (days)	58.4 (40.6)	31.3 (40.6)	0.067
Cumulative exposure ($\mu g/m^3$ days)	4606 (9.3)	6328 (9.3)	0.123
Cumulative exposure lagged 10 years ($\mu g/m^3$ days)	4057 (38.9)	2036 (38.9)	0.041
Cumulative exposure lagged 20 years ($\mu g/m^3$ days)	844 (134)	305 (134)	0.024
Average exposure ($\mu g/m^3$)	22.8 (3.4)	19.3 (3.4)	0.142
Average exposure lagged 10 years ($\mu g/m^3$)	22.6 (6.6)	12.3 (6.6)	0.0005
Average exposure lagged 20 years ($\mu g/m^3$)	10.2 (11.9)	5.3 (11.9)	0.004
Maximum exposure ($\mu g/m^3$)	32.4 (3.8)	27.1 (3.8)	0.150
Maximum exposure lagged 10 years ($\mu g/m^3$)	30.8 (7.6)	16.1 (7.6)	0.0005
Maximum exposure lagged 20 years ($\mu g/m^3$)	13.1 (13.9)	6.5 (13.9)	0.004

[a]Geometric mean.
[b]Geometric standard deviation.

between 2 and 20 $\mu g/m^3$; and >20 $\mu g/m^3$. These analyses were also lagged 10 and 20 years as was done for the quartile analyses. Although the quartile analysis did not show a monotonic increase in ORs with increasing exposure, the ORs across these categories consistently increased as exposure level increased (Table V). The ORs for the lagged average and maximum exposures, particularly a 10-year lag, were greater than for the unlagged exposures.

Lung cancer risks associated with ever being exposed to the various chemical types of beryllium encountered in the plant, and other selected exposures are presented in Table VI. With a 10-year lag, ORs were significantly associated with exposure to beryllium oxide (OR = 2.35) and beryllium–copper alloy (OR = 2.11). With a 20-year lag, ORs were significantly associated with exposure to beryllium ore (OR = 1.50), beryllium hydroxide (OR = 1.48), beryllium fluoride (OR = 1.59), beryllium oxide (OR = 1.93), and beryllium–copper alloy (OR = 1.80). The highest ORs were seen in association with exposure to beryllium oxide and beryllium–copper alloy, which were highly correlated with each other ($r = 0.995$). The production of the beryllium–copper alloy begins with the reduction of beryllium oxide, which is produced during the furnace melting and annealing operations to produce final alloy products [Sanderson et al., 2001]. Exposure–response analyses for beryllium oxide and beryllium–copper alloys showed similar patterns as those for total beryllium exposure, with higher ORs in the middle ranges of lagged exposures than in the highest (data not shown). These analyses indicated that the cases had greater lagged exposure to beryllium oxide and beryllium–copper alloy than controls, no matter which exposure parameter was observed. Few workers had ever worked in beryllium–aluminum alloy and beryllium metal-exposed jobs, and there were no apparent differences between the exposure of the cases and controls to these types of beryllium.

The frequency of ''ever exposure'' to nitric acid aerosol, fluorides, welding fume, and the metals aluminum, cadmium, copper, and nickel among cases and the odds ratios compared to the controls are also shown in Table VI. The cases tended to be more frequently exposed to acid aerosols, fluorides, copper, and welding fume; the odds ratios were significant for exposure to fluorides and copper when lagged. These exposures were common throughout the plant and highly correlated with exposure to beryllium compounds. Since the fluoride process was used at the Reading plant to extract beryllium from beryl ore, workers in the ore processing and calcining departments were exposed to airborne fluorides. Workers who melted beryllium in the arc, melt and cast, and foundry furnaces were also exposed to residual fluorides released during the extreme heating of the metal. Therefore, workers exposed to beryl ore, beryllium hydroxide, beryllium fluoride, and beryllium oxide were generally also exposed to fluorides. Since the primary product of the Reading plant was beryllium–copper alloy—created by melting beryllium with copper ingots—workers in the arc, melting and casting,

TABLE III. Comparison of the Cases and Controls by Quartiles of Various Beryllium Exposure Estimates—Exposures Lagged 0, 10, and 20 Years (Beryllium Workers Case–Control Study, USA)

Quartiles of tenure (days)					
0 Lag	Quartile ranges	≤ 65	66–298	299–1,647	>1,647
	OR	1.00	1.09	0.74	0.54*
10-Year lag	Quartile ranges	≤ 35	36–203	204–1,195	>1,195
	OR	1.00	1.64	1.28	0.87
20-Year lag	Quartile ranges	≤ 1	2–93	94–698	>698
	OR	1.00	2.23**	2.48**	1.61
Quartiles of cumulative exposure ($\mu g/m^3$ days)					
0 Lag	Quartile ranges	≤ 1,425	1,426–5,600	5,601–28,123	>28,123
	OR	1.00	0.73	0.85	0.57*
10-Year lag	Quartile ranges	≤ 808	809–3,970	3,971–20,996	>20,996
	OR	1.00	1.38	1.38	0.92
20-Year lag	Quartile ranges	≤ 20	21–2,195	2,196–12,376	>12,376
	OR	1.00	2.18**	1.89*	1.89*
Quartiles of average exposure ($\mu g/m^3$)					
0 Lag	Quartile ranges	≤ 11.2	11.3–24.9	25.0–34.0	>34.0
	OR	1.00	1.61	1.75*	1.27
10-Year lag	Quartile ranges	≤ 9.5	9.6–23.6	23.7–32.8	>32.8
	OR	1.00	2.39**	2.71**	1.83*
20-Year lag	Quartile ranges	1.0	1.1–19.3	19.4–25.5	>25.5
	OR	1.00	1.92*	3.06**	1.70
Quartiles of maximum exposure ($\mu g/m^3$)					
0 Lag	Quartile ranges	≤ 17.0	17.1–25.0	25.1–71.5	>71.5
	OR	1.00	1.82*	1.08	1.14
10-Year lag	Quartile ranges	≤ 10.0	10.1–25.0	25.1–70	>70
	OR	1.00	3.34**	2.19*	1.92*
20-Year lag	Quartile ranges	≤ 1.0	1.1–23.0	23.1–56	>56.0
	OR	1.00	1.95*	2.89**	1.67

*$P < 0.05$.
**$P < 0.01$.

and foundry furnace areas would also have been exposed to copper dust and fumes. Therefore, workers exposed to beryllium oxide and beryllium–copper alloy were also generally exposed to copper.

A total of 386 members of the Reading plant cohort had participated in the 1968 USPHS study, including nine (6.3%) of the cases and 68 (9.6%) of the controls. The number of cases and controls was too small to directly examine the association between beryllium exposure, smoking status, and risk of lung cancer. Therefore, the potential for confounding of the beryllium–lung cancer association by smoking had to be examined indirectly. In order for smoking to be a confounder in an internal analysis, there would have to be an association between smoking status and level of beryllium exposure.

Age-adjusted geometric mean tenures, cumulative exposures, average exposures, and maximum exposures of Reading plant workers in the USPHS survey, by smoking category and by professional status, are shown in Table VII. Professionals were less likely to be current smokers, and also had markedly lower exposures to beryllium than did non-professionals. Within strata there were no significant differences in age-adjusted geometric mean exposure estimates across the cigarette smoking categories for either professionals or non-professionals (Table VII). Only about 10% of the cases and 12% of the controls were professionals. In order to evaluate whether confounding by professional status was responsible for the observed exposure–response relationships, professionals were removed from the analysis. The results are very similar to those obtained with the full dataset—Tables VIII and IX compared to Tables II and III—indicating that confounding by professional status (as a surrogate for smoking) did not occur in the data.

TABLE IV. Conditional Logistic Regression Analysis of Logs of Continuous Exposure Variables (Beryllium Workers Case–Control Study, USA)

Variable	Parameter estimate	Wald statistic	*P*-value
Log tenure (days)	−0.096	5.45	0.020
Log tenure lagged 10 years (days)	0.045	2.51	0.113
Log tenure lagged 20 years (days)	0.045	4.39	0.036
Log cumulative exposure ($\mu g/m^3$ days)	−0.064	2.38	0.123
Log cumulative exposure lag 10 years ($\mu g/m^3$ days)	0.060	5.35	0.021
Log cumulative exposure lag 20 years ($\mu g/m^3$ days)	0.041	5.62	0.018
Log average exposure ($\mu g/m^3$)	0.110	2.14	0.143
Log average exposure lag 10 years ($\mu g/m^3$)	0.184	12.62	0.0004
Log average exposure lag 20 years ($\mu g/m^3$)	0.088	8.35	0.0039
Log maximum exposure ($\mu g/m^3$)	0.098	2.06	0.151
Log maximum exposure lag 10 years ($\mu g/m^3$)	0.171	12.81	0.0003
Log maximum exposure lag 20 years ($\mu g/m^3$)	0.085	8.63	0.0033

TABLE V. Comparison of Average and Maximum Exposures of Cases and Controls by Levels of Exposure—Exposures Lagged 0, 10, and 20 Years (Beryllium Workers Case–Control Study, USA)

	≤ 2	>2–20	>20
Average exposure ($\mu g/m^3$)			
Odds ratio–exposures unlagged	1.00	2.10	2.23
Odds ratio–exposures lagged 10 years	1.00	4.07**	4.17**
Odds ratio–exposures lagged 20 years	1.00	2.30**	2.19**
Maximum exposure ($\mu g/m^3$)			
Odds ratio–exposures unlagged	1.00	1.85	2.22
Odds ratio–exposures lagged 10 years	1.00	3.89**	4.58**
Odds ratio–exposures lagged 20 years	1.00	2.09*	2.34**

*$P < 0.05$.
**$P < 0.01$.

DISCUSSION

This study found that individuals who developed lung cancer had experienced higher cumulative, average, and maximum beryllium exposures 10 and 20 years before death than had controls by the same age. This is consistent with the hypothesis that beryllium is a human lung carcinogen.

The cases had lower overall tenures and cumulative exposures than the controls, but higher lagged tenures and cumulative exposures. Lagged data analyses showed significant positive exposure–response trends, while unlagged analyses did not. Most known occupational lung carcinogens cause cancer only after a latency period has passed. If beryllium acts similarly, then a latency period would be required to see an effect of exposure on disease. Thus a lag, which assumes such a latency period and discounts exposure occurring shortly before disease, would be the best way to evaluate the association between beryllium exposure and lung cancer. Lagged exposure variables would be expected to fit the data better than unlagged exposure variables—which indeed is observed. In addition to such a priori considerations, the lag essentially restricts analyses to exposures which occurred early in calendar time, in the 1940s and 1950s. This time period was generally when high exposures occurred, and when there were many short-term employees. Cases were proportionately more highly exposed in these periods, conforming to the hypothesis that beryllium causes lung cancer.

Significantly fewer cases were in the lowest average exposure and maximum exposure quartiles compared to higher exposure quartiles, indicating that the cases had higher intensity of exposure than the controls, particularly

TABLE VI. Odds Ratios for "Ever Exposed" to Various Chemical Types of Beryllium and Selected Other Agents (Beryllium Workers Case–Control Study, USA)

	0 Lag		10-Year lag		20-Year lag	
Exposure	**Cases (%)**	**OR**	**Cases (%)**	**OR**	**Cases (%)**	**OR**
Be Ore	47.9	1.07	47.9	1.27	43.0	1.50*
BeOH	48.6	1.12	47.9	1.30	42.3	1.48*
BeF	74.7	1.14	73.2	1.45	64.1	1.59*
BeO	88.7	1.52	88.0	2.35**	75.4	1.93**
BeCu	85.2	1.45	84.5	2.11**	71.8	1.80**
BeAl	4.9	0.71	4.9	0.75	4.2	0.91
Be	12.0	0.88	12.0	1.07	9.2	1.09
Acid	39.4	1.12	39.4	1.34	31.0	1.28
Aluminum	4.9	0.66	4.9	0.70	4.2	0.86
Cadmium	0	—	0	—	0	—
Copper	56.3	1.29	55.6	1.47*	48.6	1.55*
Fluorides	76.8	1.18	75.4	1.51*	66.2	1.66**
Nickel	4.9	0.66	4.9	0.70	4.2	0.86
Welding	27.5	1.06	27.5	1.25	23.2	1.27

*$P < 0.05$.
**$P < 0.01$.

TABLE VII. Age-Adjusted Exposure Estimates for Workers who Participated in the 1968 USPHS Study by Smoking Status and Professional Categories (Beryllium Workers Case–Control Study, USA)

	Current smokers GM[a] (GSD)[b]	**Ex-smokers GM (GSD)**	**Non-smokers GM (GSD)**	**All workers GM (GSD)**
Non-professionals	n = 156 (55.0%)	n = 60 (21.1%)	n = 68 (23.9%)	n = 284
Tenure (days)	4331.2 (1.9)	4801.2 (1.9)	4983.2 (1.9)	4577.7 (2.3)
Cumulative exposure ($\mu g/m^3$ days)	84,892 (3.6)	73,479 (3.6)	86,040 (3.6)	82,607 (4.0)
Average exposure ($\mu g/m^3$)	19.6 (2.8)	15.3 (2.8)	17.3 (2.8)	18.0 (2.8)
Maximum exposure ($\mu g/m^3$)	55.9 (3.3)	48.3 (3.3)	57.0 (3.3)	54.5 (1.2)
Professionals	n = 40 (39.2%)	n = 28 (27.4%)	n = 34 (33.3%)	n = 102
Tenure (days)	1684.7 (3.0)	1479.3 (3.0)	2034.2 (2.9)	1731.1 (4.0)
Cumulative exposure ($\mu g/m^3$.days)	3,709 (4.1)	2,676 (4.1)	4,621 (4.0)	3,649 (5.2)
Average exposure ($\mu g/m^3$)	2.2 (2.3)	1.8 (2.3)	2.3 (2.2)	2.1 (2.2)
Maximum exposure ($\mu g/m^3$)	3.7 (2.8)	2.5 (2.8)	3.3 (2.8)	3.2 (2.8)

[a]Geometric mean.
[b]Geometric standard deviation.

when the average and maximum exposure estimates were lagged. The majority of individuals in the cohort who developed lung cancer were employed in the 1940s and 1950s, when exposures were certainly much higher than the current occupational exposure limit of 2 $\mu g/m^3$ and current exposures in the beryllium industry. Also, tenure tended to be relatively short for workers first hired in the 1940s, especially during the war years. Average exposure predicted lung cancer better than cumulative exposure in our data, which might be expected when those with the highest exposure often had short durations of exposure. Therefore, this study is primarily able to address the effects of short-term, relatively high beryllium exposures. Because few workers had long-term exposure to high beryllium levels, the study has limited ability to observe an exposure–response relationship over a wide range of exposure levels and durations.

This study found evidence of an association between lung cancer risk and the logs of the exposure variables, particularly the intensity of exposure variables (average and

TABLE VIII. Comparison of Geometric Mean Exposures of Cases and Controls Excluding Professional Workers (Beryllium Workers Case–Control Study, USA)

	Cases n = 128	Controls n = 622	
	GM[a] (GSD)[b]	GM (GSD)	*P*-value
Tenure (days)	176 (9.9)	277 (10.0)	0.043
Tenure lagged 10 years (days)	154 (19.6)	118 (19.9)	0.360
Tenure lagged 20 years (days)	58.2 (41.1)	28.5 (41.9)	0.048
Cumulative exposure ($\mu g/m^3$ days)	4,935 (10.1)	7,182 (10.2)	0.096
Cumulative exposure lagged 10 years ($\mu g/m^3$ days)	4,228 (41.7)	2,371 (42.4)	0.111
Cumulative exposure lagged 20 years ($\mu g/m^3$ days)	991 (155.6)	347 (159.3)	0.032
Average exposure ($\mu g/m^3$)	28.0 (2.7)	25.9 (2.7)	0.435
Average exposure lagged 10 years ($\mu g/m^3$)	27.1 (6.3)	16.3 (6.4)	0.005
Average exposure lagged 20 years ($\mu g/m^3$)	12.3 (12.8)	6.7 (12.9)	0.014
Maximum exposure ($\mu g/m^3$)	39.0 (3.1)	36.3 (3.1)	0.521
Maximum exposure lagged 10 years ($\mu g/m^3$)	36.5 (7.2)	21.2 (7.3)	0.005
Maximum exposure lagged 20 years ($\mu g/m^3$)	15.7 (14.9)	8.1 (15.1)	0.012

[a]Geometric mean.
[b]Geometric standard deviation.

maximum exposure). Analyses of continuous exposure variables, which are equivalent to tests of trend, showed significant positive exposure–response trends using the log of exposure rather than exposure itself. Untransformed exposure was highly skewed, and it is not surprising that taking the logs provided a better fit to the data, a phenomenon seen in other occupational analyses of chronic disease endpoints with highly skewed data [Steenland et al., 1999]. However, no evidence of a monotonically increasing risk with increasing lagged exposure estimates was found.

One possible reason for the lack of monotonic exposure–response trends—that is tailing-off of the odds ratio in the highest quartiles of the exposure metrics—is systematic underestimation of intensity of exposures in the 1940s. This systematic underestimation might have resulted from the decision to estimate exposure levels in the 1930s and early 1940s by linear extrapolation of exposure levels estimated from the few impinger samples available between 1947 and 1953. Because exposures may have been higher during these early years when most of the cases were first employed, this may have led to an underestimation of the highest exposures encountered by workers. This could induce misclassification between the third and fourth quartiles, which in turn would tend to bias the odds ratios for the upper quartiles toward the null [Flegal et al., 1991; Correa-Vellasenor et al., 1995].

Besides misclassification of exposure, it is also possible that the apparent downturn in the exposure–response trend in the highest exposure category reflects a healthy worker survivor effect. Workers with the longest duration of exposure may have been generally healthier, allowing them to acquire greater cumulative exposure metrics, leading to an apparent lesser risk as exposure increased. Also, the flattening of lung cancer risk with increasing exposure may reflect biological saturation. That is, after particularly high beryllium exposures are obtained, increasing exposure further does not cause proportionally increased lung cancer risk [Hertz-Piccioto and Smith, 1993].

Many sources of medical information were searched to determine whether workers with previous beryllium lung disease (acute or chronic) were at an increased risk for lung cancer and whether workers with previous acute beryllium-related diseases associated with high beryllium exposures had selected themselves out of the work population. Unfortunately, medical records on the cases and controls were very limited and it was unlikely that all beryllium-associated medical problems were recorded among the Reading plant cohort. The paucity of available data provided no evidence that cases had experienced acute or chronic diseases more frequently than controls, but it is difficult to interpret such limited medical follow-up. However, the cases and controls who were documented to have had beryllium-associated diseases consistently had higher estimates of exposure than workers with no evidence they had disease, and often these differences were statistically significant. Since beryllium-associated acute diseases have usually been caused by high beryllium exposures, this sup-

TABLE IX. Comparison of the Cases and Controls by Quartiles of Various Beryllium Exposure Estimates—Exposures Lagged 0, 10, and 20 Years Excluding Professional Workers (N cases = 128; N controls = 622) Beryllium Workers Case–Control Study—USA

Quartiles of tenure (days)					
0 Lag	Quartile ranges	≤ 53	54–236	236–1,356	>1,356
	OR	1.00	0.92	0.80	0.50*
10-Year lag	Quartile ranges	≤ 30	31–155	156–950	>950
	OR	1.00	1.76*	1.45	0.84
20-Year lag	Quartile ranges	≤ 1	2–74	75–540	>540
	OR	1.00	2.52**	2.49**	1.86
Quartiles of cumulative exposure ($\mu g/m^3$ days)					
0 Lag	Quartile ranges	≤ 1,625	1,626–6,055	6,056–35,710	>35,710
	OR	1.00	0.81	0.87	0.52
10-Year lag	Quartile ranges	≤ 908	909–4,595	4,596–26,692	>26,692
	OR	1.00	1.45	1.40	0.91
20-Year lag	Quartile ranges	≤ 25	26–2,444	2,445–15,490	>15,490
	OR	1.00	2.10*	2.47**	1.63
Quartiles of average exposure ($\mu g/m^3$)					
0 Lag	Quartile ranges	≤ 16.7	16.8–25.0	25.1–42.3	>42.3
	OR	1.00	1.81*	1.36	1.03
10-Year lag	Quartile ranges	≤ 13.9	14.0–25.0	25.1–43.3	>43.3
	OR	1.00	3.63**	2.47**	1.66
20-Year lag	Quartile ranges	≤ 4.0	4.1–23.0	23.1–31.0	>31.0
	OR	1.00	2.77**	3.39**	1.76
Quartiles of maximum exposure ($\mu g/m^3$)					
0 Lag	Quartile ranges	≤ 23.0	23.1–25.1	25.2–71.5	>71.5
	OR	1.00	2.30**	0.99	1.00
10-Year lag	Quartile ranges	≤ 20.9	21.0–25.1	25.2–74.8	>74.8
	OR	1.00	3.09**	1.44	1.84*
20-Year lag	Quartile ranges	≤ 3.0	3.1–23.0	23.1–60.0	>60.0
	OR	1.00	2.23*	3.05**	1.79

*$P < 0.05$.
**$P < 0.01$.

ports the belief that exposure estimates provided by the job exposure matrix stratified workers by exposure level appropriately.

Associations between lung cancer risk and employment in specific production areas or jobs or exposure to specific chemical forms of beryllium were difficult to interpret. Few workers were exposed to some beryllium forms. The most common types of beryllium to which workers were exposed were beryllium oxide and beryllium–copper alloy, which were highly correlated with each other ($r = 0.995$). Also, workers were usually exposed to more than one type of beryllium.

Focusing the study on only one plant may be justified given the limitations of other plants with regard to work histories and exposure data. However, the small number of lung cancer cases (n = 142) makes analyses by production operation or form of beryllium difficult to interpret, because only very large differences in risk by operation and beryllium form are likely to be detected statistically given the small numbers and overlapping exposures.

The influence of exposure to other materials on lung cancer risk was also difficult to evaluate. No workers were exposed to only fluorides. Workers' exposures to fluorides and copper were also associated with lung cancer. However, exposures to these compounds were also highly associated with exposure to several beryllium compounds. Neither copper nor fluoride has evidence for carcinogenicity in animals. Copper has not been evaluated with respect to carcinogenicity by IARC; arsenic exposure is thought to be responsible for an elevated risk of lung cancer among workers employed in copper smelters [IARC, 1990]. IARC has evaluated inorganic fluorides (used in drinking water), but has not evaluated fluorides in any other form [IARC, 1987]. Fluorides have been administered in drinking water to mice and rats in an NTP bioassay. There was equivocal evidence of carcinogenic activity of sodium fluoride in male

rats based on the occurrence of a small number of osteosarcomas in treated animals [Bucher et al., 1991]. There is no suggestion that fluoride in the drinking water is linked with elevated risk of cancer [Cantor, 1997]. A recent epidemiologic study of workers exposed to fluoride in a cryolite processing plant found an increased incidence of lung cancer (standardized incidence ratio) which was neither statistically significant (95% CI = 0.94–1.88) nor related to duration of employment [Grandjean et al., 1992]. Thus, the available toxicology and epidemiologic data do not suggest that copper or fluoride are the causal agents for the observed lung cancer excess.

The major methodologic strength of the study was the exhaustive effort to document historical exposures, both by collecting all available industrial hygiene data and by evaluating the comparability of different measurement methods [Sanderson et al., 2001]. The exposure matrix was created blindly, without knowledge of the jobs and work areas where the cases were more likely to have worked. Therefore, any misclassification of exposure estimates was non-differential according to health status and would on average lead to bias toward the null, particularly when using continuous exposure metrics as in Table IV [Copeland et al., 1977; Kleinbaum et al., 1982; Checkoway et al., 1991].

On the other hand, uncertainty about the exposure matrix is also a limitation of the study, because blind assignment of exposure does not always prevent differential misclassification [Wacholder et al., 1991]. Despite an exhaustive effort to identify all available exposure data, measurements were extremely sparse for some time periods and some jobs. Assumptions that influenced large categories of exposure estimates, for example, the assumption that exposures could be extrapolated linearly from the 1950s to the 1940s, may have caused systematic misclassification of exposure for those time periods.

Although there was some evidence for potential confounding of the relationship of beryllium exposure and lung cancer by smoking, this confounding was related to professional status. The professionals smoked less and had much lower beryllium exposures than production workers, giving the appearance that higher beryllium exposures were associated with smoking. The association between beryllium exposure and lung cancer remained the same when the potential confounding was reduced by restricting the analysis to non-professionals.

The finding of an increased risk of lung cancer among workers with higher beryllium exposures when dose estimates were lagged 10 or 20 years, and lack of evidence for confounding by cigarette smoking or other factors, provides further evidence that beryllium is a human lung carcinogen. Despite extensive efforts to reconstruct historical exposures in this study, considerable uncertainty remains about exposure levels in the 1940s and 1950s and about the shape of the exposure–response curve for lung cancer. These questions may be resolved by continued follow-up of workers who entered the beryllium industry after 1970, when extensive exposure measurements began to be collected.

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